May 28, 2002

VETERINARY SERVICES MEMORANDUM NO. 800.204

Subject: General Licensing Considerations: Field Safety Studies

To: Biologics Licensees, Permittees, and Applicants
Directors, Center for Veterinary Biologics

I. PURPOSE

These general licensing considerations provide guidance to applicants for developing target animal field safety data to support an application for a U. S. Veterinary Biological Product License or U.S. Veterinary Biological Product Permit for Distribution and Sale, according to 9 CFR 102.5 or 104.5, respectively.

II. BACKGROUND

Licensing considerations provide guidance to applicants concerning the development of data in support of license applications and assist the Center for Veterinary Biologics- Licensing and Policy Development (CVB-LPD) in maintaining uniformity and consistency in the review of license applications. General Licensing Considerations address basic principles that have general application in the licensing of products. This document addresses the basic principles for conducting field safety studies.

The objective of a target animal field safety trial is to observe the effect of the product in its target population under the conditions of its intended use. It is intended to detect the types of adverse events which may occur with sufficient frequency to be seen in a trial of this scale. The field safety trial is an essential clinical component of the prelicensing process, supplementing smaller preclinical experimental studies, but not replacing ongoing postmarketing surveillance.

III. GUIDELINES

A. General Requirements

1. Permission Required - All field safety studies must meet the requirements set forth in 9 CFR 103.3 and Veterinary Services (VS) Memorandum No. 800.67. Permission to conduct a field safety study must be obtained from the CVB prior to shipping the product to the test sites. See VS Memorandum No. 800.50 for guidance on submitting a field test request to the CVB.

2. Planning and Execution - Field safety studies should be planned, executed, and documented in accordance with the general guidelines provided in VS Memorandum No. 800.200, Study Practices and Documentation.

B. Experimental Product

The experimental (pre-license) product the applicant uses for generating field safety data must accurately represent the product that the firm will produce once a product license is granted. The applicant is responsible for establishing the validity of the experimental product used to demonstrate field safety. More than one serial (numbered lot) of product should be tested. The experimental product that applicants use in field safety studies should be produced:

1. In Accordance With the Filed Outline of Production.

2. In Licensed Production Facilities - Produce the experimental product in licensed production facilities, in accordance with filed facility documents, and not in research facilities. (Production in research facilities is generally on a much smaller scale than commercial production, and the resulting products may have different properties.)

3. At or Above Release Potency - The potency of the experimental product should be at, or above, the minimum potency provided in the Outline of Production for the product.

C. Experimental Protocol

1. Content - In addition to the general information described in VS Memorandum No. 800.200, field safety study protocols should contain the following specific information:

a. The age, breed, sex, pregnancy and/or lactation status, and any other distinguishing features of animals used in the test. All types of animals that are to be included in label recommendations must be included.

b. The number of subjects to be enrolled in the study. An adequate number of animals of the minimum recommended age must be included.

c. The product must be administered as recommended on the product label, including the administration of multiple doses.

d. The product must be tested by each route of administration that is recommended on the product label. The number of animals to be used for each route of administration should be specified, and each geographical site should include groups of animals inoculated by each route.

e. When appropriate, different injection sites (e.g., neck vs. gluteal muscles in large animals, thigh vs. lumbar muscles in companion animals) should be evaluated.

f. When a product is recommended for use both in adults and in neonates, for protection of neonates (i.e., has label claims for passive and active immunity), safety must be demonstrated in an adequate number of adults and neonates.

g. The protocol must include the period of time that the animals will be observed, the frequency of observation, who will make the observations, and what follow-up work will be performed if an adverse event occurs. For live products, an acceptable period for observation must take into account the incubation period associated with the live organism(s).

h. Studies must be carried out at multiple geographic sites. Typically, three distinct sites are required. When applicable, the product should be tested under various conditions of husbandry. Data generated in countries other than the United States are generally not acceptable without prior APHIS approval.

i. Untreated control animals, which are co-mingled with treated animals, should be evaluated when live products are being tested.

j. Provide copies of the reporting form(s) and the instructions that will be issued to field investigators. The reporting system must provide for individual animal identification (or group identification for poultry).

k. The disposal of all animals used in field safety studies must be in accordance with 9 CFR 103.2.

D. Adverse Events

1. Definition - Any observation in animals that is unfavorable and unintended and occurs after the use of a veterinary product or investigational veterinary product, *whether or not considered to be product related.* This is the internationally harmonized definition promulgated by the International Cooperation on Harmonization of Technical Requirements for the Registration of Veterinary Medicinal Products (VICH).

2. Types - Adverse events may be local or systemic. When they occur, the animal should be observed until the duration of the event can be assessed. Adverse events include, but are not limited to:

a. Excessive vocalization (e.g., whining, bellowing), biting, rubbing, scratching, kicking, or licking the area of administration, when occurring within 24 hours after administration of the product.

b. Upon palpation, evidence of local pain, pain radiating from the site of administration to other areas, lameness, or soreness, which lasts more than 24 hours.

c. Anaphylaxis, Arthus reaction, lethargy, anorexia, or any change from normal or expected behavior.

d. Swelling at the injection site that is extensive and/or inflamed.

e. Formation of sterile or contaminated abscesses.

f. Enlarged regional lymph nodes or injection site abnormalities. Usually lymph nodes cannot be readily palpated. Mild hypertrophy of draining lymph nodes is considered a normal reaction to vaccination, but hypertrophy equal to, or greater than, four times the normal size must be reported. At this point, histopathological evaluation of the lesion may be warranted to define the nature of the reaction.

g. Mild steatitis at the injection site is acceptable. However, mild to severe myositis, neuritis, or perineuronal infiltration of inflammatory cells may warrant a precautionary statement on the product label.

h. Reduction in milk production

E. Reporting Requirements

1. Diagnosis - All adverse events should be diagnosed by a veterinarian and must be included in the study report.

2. Necropsy - A necropsy should be performed on all test animals that die, and the findings must be included in the study report. For poultry, daily mortality sheets and slaughter condemn reports may be submitted instead, although necropsy or diagnostic reports may be necessary to provide additional data regarding unusually high morbidity/mortality.

3. Include all animals - All animals enrolled in the study, including those excluded before the study is completed and those for which follow-up data are unavailable, must be included in the final report.

/s/ W. Ron DeHaven

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